

# **Acute d-Amphetamine alters the temporal patterning of intermittent synchronized oscillations in hippocampal and prefrontal circuits of the rat**

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## **Abstract**

D-Amphetamine (d-AMPH) increases the bioavailability of numerous catecholamines, including dopamine, throughout the brain and modulates neural firing in cortical and subcortical regions. While a complex array of d-AMPH-mediated effects on firing have been reported, less is known regarding how d-AMPH affects the oscillatory properties of cortical circuits. In the current study, we simultaneously recorded local field potentials from electrode arrays implanted in the medial prefrontal cortex (PFC) and hippocampus (HC) of awake freely moving rats treated with saline, 1.0 mg/kg, or 3.3 mg/kg d-AMPH. The fine temporal structure of synchrony in delta, theta, beta, and gamma bands between these brain regions was examined to characterize how phase synchronization was altered by each dose of d-AMPH relative to saline. Differences were observed in the average level of phase-locking and in the variation of temporal patterns of synchrony on short (sub-second) time scales (including the distribution of durations of desynchronization events). In general, treatment with d-AMPH evoked higher levels of phase-locking. While this imperfect phase-locking can be potentially attained with both large number of short desynchronization episodes and small number of long desynchronization episodes, the data are marked by the dominance of short desynchronization episodes. These results suggest that within the HC and PFC, d-AMPH acts to increase synchronized oscillatory activity. The dominance of short desynchronization episodes suggests that the synchrony can be easily destabilized, yet it can be quickly re-established. The ease with which neural circuits can transition between synchronized and desynchronized dynamics may reflect altered information transfer regimes in these circuits and contribute to the spectrum of effects on cognition frequently observed with d-AMPH.

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Detecting the temporal structure of the phase locking: Parkinson's disease and beyond

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Motor symptoms of Parkinson's disease (PD) are related to the excessive synchronized oscillatory activity in the beta band in the basal ganglia and other parts of the brain. To study this synchronization we recorded neural activity in subthalamic nucleus of awake PD patients during DBS electrode implantation surgery. The strength of phase locking of these neural oscillations varies in time. This led us to the development of methods to study this variability. These methods, their application to PD data, the models of PD brain validated by the data, and the implications for PD physiology and for DBS strategies are discussed here.

When an oscillatory system is in a weakly synchronized regime away from a synchronization threshold, it spends most of the time in parts of its phase space away from the synchronization state. Therefore characteristics of dynamics near this state (Lyapunov exponents, distributions of synchronized episodes, etc.) do not describe the system's dynamics for most of the time. We characterize the dynamics in this case by exploring the relationship between the phases on each cycle of oscillations. Synchronization is a non-instantaneous phenomenon, however if some overall level of phase locking is present, one can quantify when and for how long phase locking is lost, and how the system returns back to the phase-locked state. The obtained measures describe the temporal structure of synchronization and desynchronization events.

This approach revealed a specific character of the phase-locking in the beta band in PD: the dominance of the numerous but short desynchronization events. This suggests that even though the synchronization in PD is fragile enough to be frequently destabilized, it has the ability to reestablish itself very quickly. Using basal ganglia model we showed that the experimentally observed intermittent synchrony can be generated by moderately increased coupling strength in the basal ganglia circuits due to the lack of dopamine. Comparison of the experimental and modeling data suggest that brain activity in PD resides in the large boundary region between synchronized and nonsynchronized dynamics. Dopaminergic degeneration in PD may shift the brain networks closer to the synchronized state, which would still permit some motor behavior while accounting for motor deficits. Understanding the nature of the intermittent synchrony in PD is also important for efficient control strategies to suppress pathological synchrony through DBS.

The developed methods may also be potentially useful in other areas of neuroscience where phase locking is essential.

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Modulation of thalamocortical relay by basal ganglia in Parkinson's disease and dystonia

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Two major neurological disorders – Parkinson's disease and dystonia – are believed to involve pathology in the activity of the basal ganglia, a subcortical brain structure, whose output nuclei (internal Globus Pallidus, GPi) projects to thalamus and modulates thalamocortical relay. While these disorders may ultimately involve different network and cellular pathologies, some pathological physiology may be shared between them because surgical treatment of both conditions includes surgical lesion or electrical stimulation to GPi (pallidotomy and GPi DBS). This work compares the thalamocortical relay responses to inhibitory inputs from internal segment of GPi in Parkinson's disease and in dystonia.

Experimental data suggest that both conditions are marked by stronger oscillatory activity. In dystonia this activity becomes pathologically strong in the theta and alpha bands [1,2], while in Parkinson's disease this is the beta-band activity [3]. The activity itself is patterned in time [4], complicating the computational study of its role. To compare the modulation of thalamocortical relay, we use experimental data recorded from GPi of human subjects with Parkinson's disease or dystonia and study the difference of the quality of thalamocortical relay in these conditions following the computational setup, presented earlier in [5].

The results of the study of the “hybrid” system (computational model of TC cell modulated by experimental data) reveal a substantial similarity in the properties of relay in Parkinson's disease and in dystonia. TC relay fidelity is substantially impaired due to the pathological pattern of GPi signals in both conditions. The results are robust with respect to variations of the model details and the types of incoming excitatory synaptic input.

The results suggest that even though the rhythmicity in Parkinson's disease and dystonia are confined to different frequency bands, their effect on the dynamics of downstream circuits is similar. Thus given the differences in dystonic and parkinsonian symptoms these results suggest the existence of mechanisms beyond pathological rhythmicity and thalamocortical relay in at least in one of the conditions. On the other hand, overlap in some motor deficits of dystonia and Parkinson's disease may be attributed to the existence of similar pathological rhythmicities and the resulting deficiencies of thalamic relay.